PATENT SPECIFICATION

1,131,191

NO DRAWINGS

1,131,191

Date of Application and filing Complete Specification: 24 Jan., 1967.

No. 3518/67.

Application made in United States of America (No. 522,829) on 25 Jan., 196

Complete Specification Published: 23 Oct., 1968.

In

In

ERRATUM

SPECIFICATION No. 1,131,191
Slip No. 2

Page 1, Title, *after* "Derivatives" *delete* comma

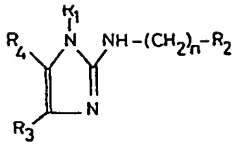
THE PATENT OFFICE
28th April 1969

ERRATUM

SPECIFICATION No. 1,131,191

Page 2, line 64, *for* "reating" *read* "reacting"

THE PATENT OFFICE
25th November 1968



(I)

and its tautomeric forms,
wherein
n represents 0, 1 or 2, and of
R_1 and R_2 one represents hydrogen while the other represents phenyl, unsubstituted, or mono- or disubstituted by, independently of each other, halogen, alkyl having at most 6 carbon atoms, alkoxy having at most 4 carbon atoms or trifluoromethyl, and
R_3 and R_4 each represent hydrogen or alkyl having at most 4 carbon atoms,
and pharmaceutically acceptable acid addition salts thereof, have not been known hitherto.

Surprisingly, it has now been found that compounds of the general formula I and their acid addition salts have valuable pharmacological properties. They show, for instance, cardio-

[Pri

... formulations include powders, creams, ointments, and solutions for topical administration. The therapeutically valuable compounds of the present invention include all physiologically acceptable acid addition salts of the imidazole derivatives characterized by general formula I. Such physiologically acceptable, non-toxic addition salts include those derived from organic and inorganic acids, such as, hydrochloric, hydrobromic, sulfuric, phosphoric, methane-sulfonic, acetic, lactic, succinic, malic, maleic, aconitic, phthalic and tartaric acids.

In the imidazole derivatives of the general formula I and in the corresponding starting materials, which are defined below, R_3 and R_4 as alkyl are, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec.-butyl, tert.-butyl, n-pentyl, isopentyl and n-hexyl.

One of R_1 and R_2 represents hydrogen, while the other is a phenyl radical which can be mono-substituted in the ortho-, meta- or para-position, e.g. by fluorine, chlorine, bromine or iodine; by methoxy, ethoxy, propoxy, isopropoxy, n-butoxy or isobutoxy; by tri-

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Index at acceptance:—C2 C(1F4C4, 1F4D2, 1F4F5, 1H1A1, 1H1A2, 1H1C3, 1H2A2, 1H2A5, 1H2A7, 1H2C2, 1H2C3, 1M1A, 1M1C2, 1Q2, 1Q3, 1Q5, 1Q6B1, 1Q6C, 1Q7A, 1Q8A, 1Q8C, 1Q9C, 1Q9E, 1Q9F1, 1Q9K, 1Q9L, 1Q11D, 1Q11G, 1Q11J, 2A3, 2A5, 2A6, 2A14, 2B38, 2D44, 2D45, 2D52, 2R15, 2T21. LH29X, LH29Y, LH32Y, LH36Y, LH220, LH250, LH252, LH321. LH322, LH364, LH662, LH670, LH680, LH682)

Int. Cl.:—C 07 d 49/36

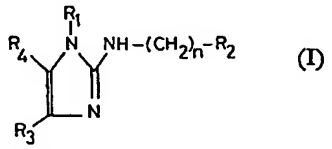
COMPLETE SPECIFICATION

New Imidazole Derivatives, their preparation and use

We, J. R. GEIGY A.G. a body corporate organised according to the laws of Switzerland, of 215, Schwarzwaldallee, Basle, Switzerland, (Assignee of NORBERT GRUENFELD), do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new imidazole derivatives and to a process for the preparation of such compounds as well as pharmaceutical preparations containing them and their administration.

Imidazole derivatives of the general formula



(I)

and its tautomeric forms,
wherein
n represents 0, 1 or 2, and of
R_1 and R_2 one represents hydrogen while the other represents phenyl, unsubstituted, or mono- or disubstituted by, independently of each other, halogen, alkyl having at most 6 carbon atoms, alkoxy having at most 4 carbon atoms or trifluoromethyl, and
R_3 and R_4 each represent hydrogen or alkyl having at most 4 carbon atoms,
and pharmaceutically acceptable acid addition salts thereof, have not been known hitherto.

Surprisingly, it has now been found that compounds of the general formula I and their acid addition salts have valuable pharmacological properties. They show, for instance, cardiovascular, analgesic, anti-inflammatory and systemic as well as local vasoconstricting activities, as well as inhibition of gastric secretion. The pharmacological results mentioned characterize compounds of the general formula I as new type of anti-inflammatory agent. The observed cardiovascular properties indicate a possible use in the treatment of shock or chronic asthenic states. These compounds may be administered parenterally or orally in any of the usual pharmaceutical forms including tablets, capsules, powders, suspensions, solutions and syrups, and also including sustained release preparations which may be compounded by any of the known procedures. Particularly valuable formulations include powders, creams, ointments, and solutions for topical administration. The therapeutically valuable compounds of the present invention include all physiologically acceptable acid addition salts of the imidazole derivatives characterized by general formula I. Such physiologically acceptable, non-toxic addition salts include those derived from organic and inorganic acids, such as, hydrochloric, hydrobromic, sulfuric, phosphoric, methane-sulfonic, acetic, lactic, succinic, malic, maleic, aconitic, phthalic and tartaric acids.

In the imidazole derivatives of the general formula I and in the corresponding starting materials, which are defined below, R_3 and R_4 as alkyl are, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec.-butyl, tert.-butyl, n-pentyl, isopentyl and n-hexyl.

One of R_1 and R_2 represents hydrogen, while the other is a phenyl radical which can be mono-substituted in the ortho-, meta- or para-position, e.g. by fluorine, chlorine, bromine or iodine; by methoxy, ethoxy, propoxy, isopropoxy, n-butoxy or isobutoxy; by tri-

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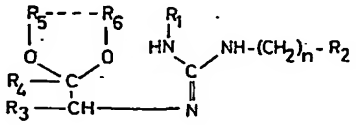
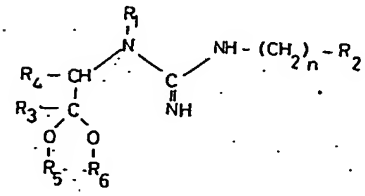
fluoromethyl or by alkyl, such as mentioned above under the illustration of R_3 and R_4, or which can be disubstituted by two different or identical radicals just mentioned, in any possible combination, as e.g. the 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-positions.

To produce the new imidazole derivatives of the general formula I and their acid addition salts, a compound of the general formula IIa or IIb.



(IIa)



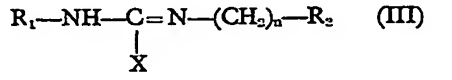
(IIb)

or a tautomeric form or acid addition salt thereof, wherein R_1, R_2, R_3 R_4 and n have the meanings given above, and R_5 and R_6 each represent alkyl having at most 6 carbon atoms or together alkylene having at most 3 carbon atoms, is cyclised by means of an acid. The product is isolated in the form of an acid addition salt or as the free base, and, if desired, the base is converted into a salt with an inorganic or organic acid. The radicals R_5 and R_6 represent, as alkyl, preferably methyl or ethyl, and as alkylene radicals, preferably ethylene or trimethylene.

This reaction can be performed in aqueous solution or in mixtures of water with solvents completely or partially miscible with water and at temperatures ranging from room temperature to the boiling point of the reaction mixture; preferably, it is carried out at slightly elevated temperature, e.g. 50°C. Mineral acids or Lewis acids in general can be used to accelerate the cyclisation reaction; a strong mineral acid such as concentrated hydrochloric acid is preferred. Due to the acidic reaction conditions, compounds of the general formula IIa or IIb will be present as salts in the reaction mixture; they can therefore be added as free bases or as salts.

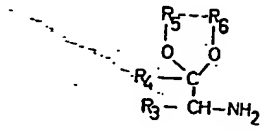
The reaction can be carried out in different modifications, i.e. compounds of the general formula IIa or IIb or salts thereof can be used as starting materials or such compounds can be formed *in situ* and cyclised without isolation and purification.

Compounds of the general formula IIa or IIb can be obtained by reacting compounds of the general formula III



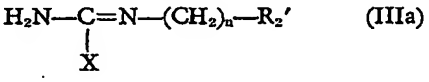
(III)

or tautomeric forms, or acid addition salts thereof,
wherein
X represents a radical which can be split off, in particular a low alkylthio or alkoxy radical, the mercapto group, the nitroso-amino radical or a substituted 1-pyrazolyl radical, and
n, R_1, R_2 have the meanings given above
with compounds of the general formula IV



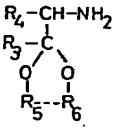
(IV)

wherein
R_3, R_4, R_5 and R_6 have the meanings given above, or by reating compounds of the general formula IIIa or tautomeric forms, or acid addition salts thereof,



(IIIa)

wherein
R_2' represents phenyl, unsubstituted, or mono- or disubstituted by, independently of each other, halogen, alkyl having at most 6 carbon atoms, alkoxy having at most 4 carbon atoms or trifluoromethyl and
n and X have the meanings given above,
with compounds of the general formula V



(V)

wherein
R_3, R_4, R_5 and R_6 have the meanings given above. These reactions can be carried out in neutral, anhydrous organic solvents, such as alkanols, e.g. absolute ethanol, at temperatures ranging from 0°C to elevated temperatures. The reaction usually is completed by heating to reflux for several hours.

Another way for the production of starting materials of the general formula IIa or IIb starts from compounds of the general formula VIa or VIb

$$R_1'—NH—C\equiv N \qquad (VIa)$$

$$R_2'—(CH_2)_a—NH—C\equiv N \qquad (VIb)$$

wherein

R_1' and R_2' represent phenyl, unsubstituted, or mono- or disubstituted by, independently of each other, halogen, alkyl having at most 6 carbon atoms, alkoxy having at most 4 carbons or trifluoromethyl.

Compounds of the general formula VIa are reacted with compounds of the general formula IV. Compounds of the general formula VIb can be reacted with compounds of the general formula IV or V. This reaction can be carried out in inert, anhydrous organic solvents, such as hydrocarbons, e.g. absolute benzene, at temperatures of about 50—100°C, preferably at the reflux temperature of the reaction mixture, i.e. at about 80°C, when benzene is used as solvent.

Many compounds of the general formulae III, IV, V, VIa and VIb are either known *per se* or others can be produced in a known manner starting from known compounds.

Compounds of the general formula III, wherein X represents the methylthio group are obtained by methylation with, e.g., methyl iodide of the corresponding thiourea, which in its turn is the product of the reaction between an amine and an isothiocyanate substituted corresponding to the meanings of R_1 and R_2.

Compounds of the general formula IV and V are obtained by ketal- or acetal-formation of the corresponding α-amino-ketone or α-amino-aldehyde which can be produced, e.g., by exchanging the halogen atom of the corresponding α-halo-ketone or α-halo-aldehyde by the amino group.

Compounds of the general formula VIa and VIb can be obtained from the corresponding thioureas by treatment with strong bases and metal salts like, e.g., lead acetate, mercuric acetate or cupric sulfate.

Another embodiment of the present invention is the use of pharmaceutical compositions comprising at least one physiologically acceptable inert carrier or diluent and an amount of a compound of the present invention sufficient to exhibit anti-inflammatory and/or cardiovascular activity. The proportion of a compound of the present invention incorporated into the carrier ranges from about 10 to about 90 parts by weight per 100 parts of carrier material.

To produce dosage units for peroral application, the compositions of this invention may be combined, e.g., with solid pharmaceutically acceptable pulverulent carriers such as lactose, saccharose, sorbitol or mannitol; starches such as potato starch, corn starch or amylopectin, and also laminaria powder or citrus pulp powder; cellulose derivatives or gelatine; also lubricants such as magnesium or calcium stearate or polyethylene glycols (Carbowaxes) [Registered Trade Mark] of suitable molecular weights may be added, to form tablets or press-coated tablets. The latter are coated for example, with concentrated sugar solutions which can contain, e.g., gum arabic, talcum and/or titanium dioxide, or they are coated with a lacquer dissolved in easily volatile organic solvents or a mixture of organic solvents. Dyestuffs can be added to these coatings, for example, to distinguish between different contents of active substance.

Hard gelatine capsules contain, for example granulates of the instant compositions with solid, pulverulent carriers such as, e.g. lactose, saccharose, sorbitol, mannitol, and further starches such as potato starch, corn starch or amylopectin, cellulose derivatives or gelatin, as well as magnesium stearate or stearic acid.

Suppositories containing a compound of the present invention are readily obtained by techniques well known to those skilled in the art of compounding dosage forms. A compound of the present invention is dispersed in a carrier such as cocoa butter, and the suppositories are formed in the usual way.

The following examples are given by way of illustrating the instant invention. They are not to be construed as limiting the scope thereof in any way. The temperatures are given in degrees Centigrade.

EXAMPLE 1.

1 - (p - Methoxyphenyl) - 2 - aminoimidazole Hydrochloride

Crude 1 - (*p* - methoxyphenyl) - 3 - (β,β-diethoxyethyl)-guanidinium iodide (59.5 g, $n_D^{24}=1.57$) was dissolved in 250 ml of concentrated hydrochloric acid and the solution was heated at 50° for 1 hour. The acid solution was cooled, diluted with water, washed several times with ether, and reduced to a small volume under vacuum. The solution was rendered basic with saturated sodium carbonate solution to pH 9 and was repeatedly extracted with chloroform. The chloroform solution was washed with a small volume of water, dried over sodium sulfate and evaporated to dryness to yield a semi-solid (25.6g). Recrystallization from ethyl acetate gave higher melting crude product (m.p. 153—156°); a second crop of lower melting impure product (m.p. 121—129°) was also obtained. The higher melting product was dissolved in isopropanol, the solution was cooled and 4.5 ml of 7.5 N ethanolic hydrochloric acid was added whereupon the hydrochloride (m.p. 222—225° dec.) crystallized. The lower melting mixture (m.p. 121—129°) also yielded some desired hydrochloride (m.p. 219—223° dec.). Two recrystallizations from isopropanol (charcoal) gave the desired compound (m.p. 225—227° with decomposition).

1-(p-Methoxyphenyl)-2-aminoimidazole

1 - (*p* - Methoxyphenyl) - 2 - aminoimidazole hydrochloride (0.5 g) was dissolved in

water (10 ml). The pH was adjusted to 9 with saturated sodium carbonate solution and the product was extracted repeatedly with chloroform. The chloroform extract was washed with a little water, dried over sodium sulfate and evaporated to dryness to give the title product (m.p. 160—163°).

The starting material used in this example was obtained as follows:

1 - (p - Methoxyphenyl) - 3 - (β,β - diethoxyethyl)guanidinium Iodide

p - Methoxyphenyl - S - methyl - isothiuronium iodide (0.139 mole, 45 g) was dissolved in dry ethanol (140 ml). The solution was cooled and aminoacetaldehyde diethyl acetal (0.139 mole, 18.5 g) was added dropwise while stirring. The solution was heated under reflux for 3 hours and evaporated to dryness to give an oil (59.5 g, $n_D^{24.0} = 1.57$).

Example 2.

1-Phenyl-2-aminoimidazole Hydrochloride

A solution of 1-phenyl-3-(β,β-diethoxyethyl-guanidinium iodide (crude, 37.8 g) in 100 ml of concentrated hydrochloric acid was heated at 50° for one hour. Water (300 ml) was added, and the solution was extracted with ether. The aqueous solution was rendered basic to pH9 with saturated sodium carbonate solution and repeatedly extracted with chloroform after saturating with sodium chloride. The chloroform solution was washed with water, dried over sodium sulfate and evaporated to dryness. The residue was dissolved in isopropanol (100 ml) and ethanolic hydrochloric acid (12 ml, 8N) was added. Re-evaporation to dryness gave semi-solid which was recrystallized from isopropanol (75 ml) to give desired compound (m.p. 206—209°). Two recrystallizations from isopropanol (charcoal) gave the desired compound (m.p. 213—215°).

1-Phenyl-2-aminoimidazole

The above hydrochloride (0.5 g) was converted to the free base by extraction from alkaline solution (pH 9) with chloroform. Impure 1-phenyl-2-aminoimidazole (m.p. 117—121°) was obtained.

The starting material used in this example was obtained as follows:

1 - Phenyl - 3 - (β,β - diethoxyethyl)guanidinium Iodide

Aminoacetaldehyde diethylacetal (0.1 mole, 13.3 g) was added dropwise to a cooled suspension of phenyl-S-methyl-isothiouronium iodide (0.1 mole, 29.4 g) in anhydrous ethanol. The solution was heated under reflux for three hours, and evaporated to dryness to give an oil (41.30 g $n_D^{24} = 1.5620$).

Example 3.

1 - (p - Methoxyphenyl) - 5 - methyl - 2-aminoimidazole Hydrochloride

Crude 1 - (*p* - methoxyphenyl) - 3 - [α-(β,β-ethylenedioxypropyl)]guanidinium iodide (36.3 g) was dissolved in isopropanol (100 ml); concentrated hydrochloric acid (50 ml) was added while cooling and the resulting solution was heated at 50° for 1½ hours. Isopropanol was removed under reduced pressure; water (150 ml) was added; the aqueous solution was washed with ether, evaporated to a small volume under reduced pressure, made basic (to pH 9) with saturated sodium carbonate solution and extracted with chloroform (4 × 300 ml). The chloroform solution was washed with water, dried over sodium sulfate and evaporated to dryness to give an oil. This was dissolved in isopropanol and treated with ethanolic hydrochloric acid (16.5 ml, 8.5 N); the resulting solution was again evaporated to dryness. The residue was suspended in ethyl acetate (150 ml).

A semi-solid was formed on storage in the refrigerator for two days. The ethyl acetate was decanted; the residue was dried under reduced pressure and suspended in acetone (100 ml). The resulting solid was collected (m.p. 209—211°). This was combined with the identical product from other batches and reconverted to the free base (m.p. 146—148°). Reconversion to the hydrochloride salt (as described above) yielded the desired compound (m.p. 210—212°). Recrystallization from isopropanol yielded the desired compound (m.p. 210—212°).

The starting material used in this example was obtained as follows:

1 - (p - Methoxyphenyl) - 3 - α - (β,β-ethylenedioxypropyl)guanidinium Iodide

Aminoacetone ethylene ketal (0.091 mole, 10.65 g) was added dropwise to a cooled suspension of p-methoxyphenyl - S - methyl - isothiuronium iodide (see example 1; 0.091 mole, 29.6 g) in absolute ethanol (100 ml). The resulting solution was heated under reflux for 3 hours, filtered to remove insoluble material and evaporated to dryness to give an oil (36.3 g).

Example 4.

2-(p-Fluorophenylamino)-imidazole

A solution of 1-*p*-fluorophenyl-3-(β,β-diethoxyethyl)guanidinium iodide (crude, 45 g) in concentrated hydrochloric acid (150 ml) was heated at 50° for 1 hour. The resulting solution was washed with ether, evaporated to a small volume under reduced pressure, rendered basic to pH 9 with saturated sodium carbonate solution and repeatedly extracted with chloroform. The chloroform-insoluble, water insoluble material was filtered off (m.p. 173—179° dec.). The chloroform extract was washed with water, dried over sodium sulfate and evaporated to dryness to give an oil. This was dissolved in a small volume of benzene; additional product (m.p. 171—178° dec.) crystallized. The mother liquor was evaporated to dryness (see example 5). Sublimation of a small sample at 120°/0.05 Torr gave the compound (m.p. 174—176° with decomposition).

2 - (p - Fluorophenylamino) - imidazole Hydrochloride

2-(*p*-Fluorophenylamino)-imidazole (4.1 g) was dissolved in isopropanol; the solution was treated with charcoal. Ethanolic hydrochloric acid (7.5 N, 3.1 ml) was added, and the resulting solution was evaporated to dryness. The residue was treated with charcoal in isopropanol and was twice recrystallized from isopropanol — ethyl acetate (1:4 by volume), (50 ml) to give the desired compound (m.p. 175—178°).

The starting material used in this example was obtained as follows:

p - Fluorophenyl - S - methyl - isothiuronium Iodide

Methyl iodide (0.126 mole, 17.9 g) was added dropwise while stirring to an ice cooled suspension of *p*-fluorophenyl-thiourea (0.12 mole, 20.4 g) in dry ethanol (60 ml). The reaction mixture was stirred at room temperature overnight; complete solution occurred within an hour. The reaction mixture was evaporated to dryness, and suspended in anhydrous benzene; slow crystallization yielded 36.1 g of product (m.p. 147—150°).

1 - (p - Fluorophenyl) - 3 - ($\beta_x\beta$ - diethoxyethyl) guanidinium Iodide

Aminoacetaldehyde diethylacetal (0.11 mole, 14.63 g) was added dropwise to an ice-cooled solution of *p*-fluorophenyl-S-methyl-isothiuronium iodide (0.11 mole, 34.32 g) in dry ethanol (110 ml). The reaction mixture was heated under reflux for 3 hours, stirred at room temperature overnight and subsequently evaporated to dryness to give an oil (45.70 g, $n_D^{24}=1.55$).

EXAMPLE 5.

1 - (p - Fluorophenyl) - 2 - aminoimidazole Hydrochloride

A solution of 1-(*p*-fluorophenyl)-3-($\beta_x\beta$-diethoxyethyl)-guanidinium iodide (crude, 45 g, see example 4) in concentrated hydrochloric acid (150 ml) was heated at 50° for 1 hour. The resulting solution was washed with ether, evaporated to a small volume under reduced pressure, rendered basic to pH 9 with saturated sodium carbonate solution and repeatedly extracted with chloroform. The chloroform-insoluble, water-insoluble material was filtered off (m.p. 173—179° dec.). The chloroform extract was washed with water, dried over sodium sulfate and evaporated to dryness to give an oil. This was dissolved in a small volume of benzene; additional product (m.p. 171—178° dec.) crystallized. The mother liquor was evaporated to dryness. The residue was dissolved in isopropanol (50 ml) and treated with charcoal. Ethanolic hydrochloric acid (7.5 N, 13 ml) was added and the solution was evaporated to dryness. Crystallization from isopropanol (40 ml) gave the title compound (m.p. 239—244°). Two recrystallizations from isopropanol (charcoal) gave the desired compound (248—250° with decomposition).

EXAMPLE 6.

1 - Phenyl - 5 - methyl - 2 - aminoimidazole Hydrochloride

Crude 1 - phenyl - 3 - α - ($\beta_x\beta$ - ethylenedioxypropyl)-guanidinium iodide (36.6 g) was dissolved in 50 ml of conc. hydrochloric acid, and this solution was stirred at 50° for one hour. Water (30 ml) was added; the aqueous solution was repeatedly washed with ether, and evaporated to almost dryness. Saturated sodium carbonate solution was added. The basic solution (pH 9) was repeatedly extracted with chloroform (5 x 200 ml). The chloroform extract was washed with water, dried over sodium sulfate and evaporated to dryness. The residue was dissolved in isopropanol (100 ml); the solution was cooled and ethanolic hydrochloric acid (7.5 N, 12.5 ml) was added. The solution was evaporated to 50 ml, and the product crystallized (m.p. 253—257°). Recrystallization from isopropanol (charcoal) gave the desired compound (m.p. 260—263° with decomposition).

The starting materials used in this example were obtained as follows:

1 - Phenyl - 3 - α - ($\beta_x\beta$ - ethylenedioxypropyl)-guanidinium Iodide

Aminoacetone ethylene ketal (0.1 mole, 11.70 g) was added dropwise to a cooled suspension of phenyl-S-methylisothiuronium iodide (0.1 mole, 29.40 g) in anhydrous ethanol (100 ml). The solution was heated under reflux for three hours and evaporated to dryness to give an oil (41.30 g $n_D^{24}=1.59$). This was redissolved in methylene chloride. The insoluble material was removed by filtration, and the solution was re-evaporated to dryness to give an oil (36.6 g).

Aminoacetone ethylene Ketal

This compound was obtained by reacting potassium phthalimide and 1-chloropropanone in anhydrous benzene. The resulting N-acetonylphthalimide was condensed with ethylene glycol in anhydrous benzene, using p-toluenesulfonic acid as catalyst. Phthalimidoacetone ethylene ketal, so obtained was treated with hydrazine hydrate in water. This conversion can also be carried out by saponification with 25% aqueous potassium hydroxide or by refluxing with excess n-butylamine in methanol.

EXAMPLE 7.

2-(o-Chlorobenzylamino)-imidazole

A solution of 1-(*o*-chlorobenzyl)-3-($\beta_x\beta$-diethoxyethyl)guanidinium iodide (136 g) in isopropanol (200 ml) and concentrated HCl (300 ml) was heated at 50° for 1 hour. The resulting solution was evaporated to a small volume under reduced pressure; the aqueous solution was washed with ether, rendered basic to pH 9 with saturated sodium carbonate solu-

tion and extracted several times with chloroform. The chloroform extract was washed with water, dried over sodium sulfate and evaporated to dryness to give an oil which was dissolved in isopropanol. Ethanolic HCl (51 ml, 7.5 N) was added while cooling and the resulting solution was re-evaporated to dryness. An isopropanol solution was treated with charcoal and the product was crystallized from isopropanol-ethyl acetate (1:6 by volume) (m.p. 183—189°). This was dissolved in water, the aqueous solution was filtered, treated with charcoal, washed with ether and rendered basic to pH 9 with saturated sodium carbonate solution. The product that precipitated (m.p. 173—175°) was first washed with water, and subsequently with chloroform.

2-(o-Chlorobenzylamino)-imidazole Hydrochloride

A solution of 2-(*o*-chlorobenzylamino)imidazole (11.3 g) in isopropanol was filtered, cooled, treated with ethanolic hydrochloric acid (8.5 N, 7.65 ml) and evaporated to dryness. The residue was recrystallized from isopropanol (charcoal) to give the desired product (m.p. 204—207°). One additional recrystallization from isopropanol (charcoal) yielded the pure desired compound (m.p. 204—206°).

The starting material used in this example was obtained as follows:

o - Chlorobenzyl - S - methyl - isothiuronium Iodide

Methyl iodide (0.15 mole, 9.33 ml) was added dropwise to an ice-cooled mixture of *o*-chlorobenzyl thiourea (0.13 mole, 25.27 g) in ethanol (anhydrous, 60 ml). After the addition was complete, the solution was heated under reflux for one hour and evaporated to dryness. The residue (m.p. 108—113°) was suspended in ethyl acetate (ca. 150 ml), stored at room temperature overnight and filtered. Yield: 45.5 g, m.p. 113—117°.

1 - o - Chlorobenzyl) - 3 - (β,β - diethoxyethyl)guanidinium Iodide

Aminoacetaldehyde diethylacetal (0.3 mole, 40.2g) was added dropwise to an ice-cooled suspension of o-chlorobenzyl-S-methyl-isothiuronium iodide (0.3 mole, 102.5 g) in absolute ethanol (300 ml). The resulting solution was heated under reflux for 3 hours and evaporated to dryness to give the crude guanidinium compound (136 g).

EXAMPLE 8.

1-(o-Chlorophenyl)-2-aminoimidazole

A solution of crude 1-(*o*-chlorophenyl)-3-(β,β-diethoxyethyl)guanidine (21.7 g) in concentrated hydrochloric acid (75 ml) was heated at 50° for 1 hour. Water (75 ml) was added and the aqueous solution was washed with ether. The aqueous solution was evaporated to a small volume, rendered alkaline to pH 9 with saturated sodium carbonate solution and extracted with chloroform. The chloroform extract was washed with water, dried over sodium sulfate and evaporated to dryness. The crude product was chromatographed over Florisil [Registered Trade Mark] (140 g). Elution with chloroform (1500 ml) gave 2-(*o*-chloroanilino)-imidazole (m.p. 107—117°) (see example 9). Further elution with chloroform (1000 ml) gave an oil. Elution with additional chloroform (1000 ml), chloroform — 1% by volume methanol (1500 ml), and chloroform — 3% by volume methanol (500 ml) gave the crude 1-(*o*-chlorophenyl)-2-aminoimidazole (m.p. about 150°). Recrystallization from benzene gave purer product (m.p. 166—169°). One additional recrystallization from isopropanol yielded the desired compound (m.p. 168—170°).

The starting material used in this example was obtained as follows:

1 - (o - Chlorophenyl) - 3 - (β,β - diethoxyethyl)guanidine

A solution of *o*-chlorophenyl cyanamide (0.075 mole, 11.4 g) and aminoacetaldehyde diethylacetal (0.075 mole, 9.9 g) in anhydrous benzene (150 ml) was heated under reflux for 3 hours. The resulting solution was evaporated to dryness to give a crude product (21.7 g).

EXAMPLE 9.

2-(o-Chlorophenylamino)-imidazole

A solution of crude 1-(*o*-chlorophenyl)-3-(β,β-diethoxyethyl)guanidine (21.7 g, see example 8) in concentrated hydrochloric acid (75 ml) was heated at 50° for 1 hour. Water (75 ml) was added and the aqueous solution was washed with ether. The aqueous solution was evaporated to a small volume, rendered alkaline to pH 9 with saturated sodium carbonate solution and extracted with chloroform. The chloroform extract was washed with water, dried over sodium sulfate and evaporated to dryness. The crude product was chromatographed over Florisil (140 g). Elution with chloroform (1500 ml) gave product (m.p. 107—117°). Recrystallization from benzene gave a purer product (m.p. 126—129°). One additional recrystallization from benzene yielded the desired compound (m.p. 125—127°).

2-(o-Chlorophenylamino)-imidazole Hydrochloride

A solution of 2-(*o*-chlorophenylamino)-imidazole (1.25 g, crude) in isopropanol (25 ml) was first treated with charcoal and subsequently reacted with ethanolic hydrochloric acid (8.5N, 1.1 ml) while cooling in an ice-bath. The resulting solution was evaporated to dryness, and the residue was recrystallized from isopropanol-isopropyl ether (1:1 by volume) to give the desired compound (m.p. 175—177°).

An additional recrystallization from isopropanol-ethyl acetate (1:2 by volume) gave the pure product (m.p. 176—178° dec.).

EXAMPLE 10.

2 - (o,o' - Dichlorophenylamino) - imidazole Hydrochloride

A solution of crude *o,o'*-dichlorophenylcyanamide (20 g) and aminoacetaldehyde diethylacetal (0.083 mole, 11.0 g) in anhydrous benzene was heated under reflux for two hours. The solution was filtered and evaporated to dryness to give crude guanidine (27.6 g). A solution of the above in concentrated hydrochloric acid (140 ml) was heated at 50° for 1 hour. Water (140 ml) was added; the solution was filtered hot to remove insoluble material, was washed with ether, and evaporated to a small volume under reduced pressure. A crude product (m.p. 251—258°) precipitated and was removed by filtration. This was recrystallized from isopropanol (charcoal, 40 ml) to give purer desired product (m.p. 276—278° dec.). The mother liquor was rendered basic to pH 9 with saturated sodium carbonate solution. Insoluble material was filtered off (free base of title product, m.p. 224—229°) and washed with a little chloroform. This was dissolved in isopropanol, treated with ethanolic hydrochloric acid (3.0 ml, 8.5 N) and the resulting solution evaporated to dryness to give the crude title product (m.p. 268—272° dec.). Two recrystallizations from isopropanol (charcoal) gave a purer product (m.p. 269—272° dec.). This was combined with the batch obtained first (m.p. 276—278° dec.) and recrystallized from isopropanol to give the desired compound (m.p. 273—274° dec.).

2-(o,o'-Dichlorophenylamino)-imidazole

2-(*o,o'*-Dichlorophenyl)-imidazole hydrochloride (2.3 g) was dissolved in hot water, the solution was filtered, and rendered basic to pH 9 with saturated sodium carbonate solution. The product (m.p. 225—228°) precipitated.

The starting material used in this example was obtained as follows:

o,o'-Dichlorophenyl-cyanamide

A boiling solution of potassium hydroxide (85%, 99 g) in water (240 ml) was added to a boiling suspension of *o,o'*-dichlorophenylthiourea (0.15 mole, 33.2 g) in water (240 ml). The resulting solution was immediately treated with a hot saturated solution of lead acetate trihydrate (62.7 g), adding it in a rapid stream with vigorous stirring. The resulting mixture was boiled for 6 minutes, and then cooled to 0° in salt-ice bath. The lead sulfide was filtered off with suction and washed with 100 ml of boiling 5% aqueous potassium hydroxide solution. The filtrate was acidified with glacial acetic acid (108 ml), while maintaining the temperature at 0—5°. The resulting solid was removed by filtration (m.p. 250—265°). The resulting product was boiled with methylene chloride (300 ml); the insoluble material (6.1 g, m.p. 271—280°, not desired product) was removed by filtration and the methylene chloride solution was evaporated to dryness to give the impure cyanamide (20 g, m.p. 93—118°).

EXAMPLE 11.

2 - [*β* - (m,p - Dimethoxyphenyl) - ethylamino]-imidazole

Aminoacetaldehyde diethylacetal (0.01 mole, 1.33 g) was added dropwise to a suspension of *β* - (*m,p* - dimethoxyphenyl) - ethyl - S-methyl-isothiuronium iodide (0.01 mole, 3.82 g) in absolute ethanol (10 ml). The mixture was heated under reflux for 64 hours and the resulting solution was evaporated to dryness to give an oil (4.95 g). This was dissolved in concentrated hydrochloric acid (10 ml) and isopropanol (7 ml). The solution was heated at 50° for ½ hour and water (10 ml) was added. The aqueous solution was washed with ether, rendered basic to pH 9 with saturated sodium carbonate solution and extracted with chloroform (3 × 50 ml). The chloroform extract was washed with water, dried over sodium sulfate and evaporated to dryness to give an oil. This was dissolved in isopropanol; ethanolic hydrochloric acid (7.1 N, 1.7 ml) was added with cooling. The solution was evaporated to dryness; the residue was dissolved in water. The aqueous solution was treated with charcoal, washed with ether, rendered basic to pH 9 with saturated sodium carbonate solution and extracted with chloroform to give an oil. This was chromatographed over Florisil (10 g), eluting first with methylene chloride (ca. 250 ml) to give an oil. Further elution with methylene chloride-chloroform (1:1 by volume) (600 ml) gave a cleaner oil. This was crystallized from benzene (charcoal) to give the title compound (m.p. 112—114°).

The starting materials used in this example were obtained as follows:

β-(m,p-Dimethoxyphenyl)-ethyl isothiocyanate

A solution of *β*-(*m,p*-dimethoxyphenyl)-ethylamine (0.20 mole, 36.2 g) in chloroform (50 ml) was added dropwise to an ice-cooled mixture of thiophosgene (0.20 mole, 23.0 g), calcium carbonate (0.28 mole, 28.0 g), water (65 ml) and chloroform (65 ml), agitated vigorously with a vibromixer. After the addition was complete, the mixture was heated at 35—40° for three hours with vigorous agitation. The reaction mixture was cooled, filtered and the salts were well washed with chloroform; the pH was adjusted to 8 with saturated sodium carbonate solution, the chloroform layer was separated and the aqueous layer was further extracted with chloroform. The combined chloroform extract was washed with water, dried over sodium sulfate and evaporated to dryness. The residue was twice distilled to give the pure isothiocyanate (25 g, b.p. 140—145°/0.2 Torr, $n_D^{24}=1.5873$).

β - (m,p - Dimethoxyphenyl) - ethyl - thiourea

A solution of β-(*m,p*-dimethoxyphenyl)ethyl-isothiocyanate (33.0 g) in benzene (200 ml) was added dropwise to an ice-cooled saturated solution of ammonia in anhydrous benzene (400 ml). Anhydrous ammonia was subsequently passed through the reaction mixture with stirring and cooling for 5 hours. The reaction mixture was stirred overnight, and the product that precipitated was collected (yield: 27.5 g, m.p. 161—163°). Recrystallization of a 5.0 g sample from ethanol gave an analytical sample of the desired product (4.73 g, m.p. 160—162°).

β - (m,p - Dimethoxyphenyl)ethyl - S - methyl isothiuronium Iodide

A solution of β-(*m,p*-dimethoxyphenyl)-ethylthiourea (26.6 g), methyl iodide (23.56 g) in ethanol (absolute, 100 ml) was stirred at 50° for 3 hours. The suspension was cooled, and the product was collected on a Buchner funnel (yield: 38.24 g, m.p. 140—142°). Recrystallization from isopropanol gave an analytical sample of the desired product (m.p. 140—142°).

EXAMPLE 12.

2 - (o - Chlorophenylamino) - 4,5 - dimethyl-imidazole Hydrochloride

A solution of crude 1-(*o*-chlorophenyl-3-β-(γ,γ - ethylenedioxybutyl) - guanidine (23.9 g) in concentrated hydrochloric acid (240 ml) was heated at 60° for a half-hour. The solution was cooled, water (240 ml) was added; the aqueous solution was washed with ether, and evaporated to a small volume (100 ml) under reduced pressure. This was cooled, rendered alkaline to pH 8—9 with saturated sodium carbonate solution and extracted with chloroform (3 × 500 ml). The chloroform extract was washed with water, dried over sodium sulfate and evaporated to dryness to give an oil. This was dissolved in isopropanol (250 ml), the solution was filtered, treated with ethanolic hydrochloric acid (8N, 11 ml) and evaporated to dryness under reduced pressure. The residue was redissolved in isopropanol, the solution was twice treated with charcoal and re-evaporated to dryness. The residue was crystallized from isopropanol-ethyl acetate (1:20 by volume) to give the product (m.p. 193—195° dec.). This was redissolved in isopropanol, again treated with charcoal and the solution was evaporated to dryness. Two recrystallizations from isopropanol-ethyl acetate (1:9 by volume) gave a screening sample of the product (m.p. 200—201°).

The starting materials used in this example were obtained as follows:

1 - (o - Chlorophenyl) - 3 - β - (γ,γ - ethylene-dioxybutyl)-guanidine

A mixture of *o*-chlorophenyl-cyanamide (0.087 mole, 13.31 g) and 3,3-ethylenedioxy-2-butylamine (0.087 mole, 11.4 g) in anhydrous benzene (400 ml) was stirred under reflux for 15 hours. The reaction mixture was cooled to room temperature and insoluble material (1.2 g, m.p. 252—255°) was removed by filtration. The mother liquor was evaporated to dryness to give crude product (17.8 g) which was directly hydrolyzed. Addition of a solution of *o*-chlorophenyl cyanamide in benzene to a solution of 3,3-ethylenedioxy-2-butylamine in benzene led to the immediate precipitation of a compound (m.p. 114—115°), apparently the amine salt of *o*-chlorophenyl cyanamide.

3,3-Ethylenedioxy-2-butylamine

This compound was obtained in a manner similar to that described for aminoacetone ethylene ketal in example 6, i.e. 3-phthalimido-2,2-ethylenedioxybutane, obtained from 3-phthalimido-2-butanone and ethylene glycol, was hydrolysed with 25% aqueous potassium hydroxide.

EXAMPLE 13.

2-(p-Chlorobenzylamino)-imidazole

A solution of 1-(*p*-chlorobenzyl)-3-(β,β-diethoxyethyl)-guanidinium iodide (2.0 g) in concentrated hydrochloric acid (4.5 ml) was heated at 50° for 1 hour. Water (4.5 ml) was added; the resulting solution was washed with ether, evaporated to a small volume under reduced pressure, rendered basic to pH 9 with saturated sodium carbonate solution and extracted with chloroform. The chloroform extract was washed with water, dried over sodium sulfate and evaporated to dryness to give an oil. This was dissolved in isopropanol; the solution was treated with charcoal and subsequently with ethanolic hydrochloric acid (8.5N, 0.6 ml). The resulting solution was evaporated to dryness to give an oil. This was dissolved in water. The solution was washed with ether, rendered basic to pH 8.5—9 with saturated sodium carbonate solution and extracted with chloroform. The chloroform extract was dried over sodium sulfate and evaporated to dryness to give a semi-solid (M.P. 102—116°). This was suspended in hexane; hexane was removed by decantation and the residue was recrystallised from benzene (charcoal) to give the desired compound (M.P. 122—125°). This material was recrystallised from benzene to give a purer compound (M.P. 128—130°).

2 - (p - Chlorobenzylamino) - imidazole Hydrochloride

2 - (*p* - Chlorobenzylamino) - imidazole (1.6 g) was dissolved in isopropanol (50 ml) and ethanolic hydrochloric acid 8.0N, 5.0 ml) was added with cooling. The resulting solution was evaporated to dryness and the residue was crystallised from ethyl acetate (M.P. 140—144°). Two recrystallisations from isopropanol-ethyl acetate (1:2 by volume) gave a screen-

ing sample of the desired product (M.P. 143—145°).

The starting materials used in this example was obtained as follows:

p-Chlorobenzyl-S-methyl isothiuronium Iodide

A mixture of *p*-chlorobenzyl-thiourea (0.1 mole, 20.1 g) and methyl iodide (0.15 mole, 9.3 ml) in absolute ethanol (50 ml) was stirred at room temperature for 2 hours, and evaporated to dryness to give an oil (34.26 g) which crystallised slowly from ethyl acetate to give the desired compound (approximately 25.0 g, M.P. 104—108°).

1 - (p - Chlorobenzyl) - 3 - (β,β - diethoxyethyl)-guanidinium Iodide

Aminoacetaldehyde diethylacetal (0.005 mole, 0.67 g) was added to an ice-cooled suspension of *p*-chlorobenzyl-S-methyl-isothiuronium iodide (0.005 mole, 1.71 g) in dry ethanol (5 ml). The resulting solution was heated under reflux for 3 hours and evaporated to dryness under reduced pressure to give an oil (2.1 g, $n_D^{24} = 1.54$).

EXAMPLE 14.

2 - (o - Chloro - m' - trifluoromethylphenylamino)-imidazole Hydrochloride

A solution of crude 1-(*o*-chloro-*m*'-trifluoromethylphenyl) - 3 - (β,β - diethoxyethyl)-guanidine (24.6 g) in concentrated hydrochloric acid (50 ml) was heated at 50° for one hour. Water (50 ml) was added; the mixture was washed with ether, and water-ether insoluble material was removed by filtration. The aqueous solution was evaporated to a small volume under reduced pressure; additional water (50 ml) was added, the solution was treated with charcoal, rendered basic to pH 9 with saturated sodium carbonate solution. The resulting precipitate (semi-solid) was removed by filtration, and washed with water; it was then dissolved in chloroform. The chloroform solution was washed with water, dried over sodium sulfate and evaporated to dryness to give an oil. This was dissolved in isopropanol (25 ml), the solution was cooled in an ice-bath and ethanolic hydrochloric acid (7.1N, 7.0 ml) was added. The resulting solution was evaporated to dryness. An isopropanol solution of the residue was treated with charcoal and was re-evaporated to dryness. Crystallization from boiling ethyl acetate gave impure product (m.p. 194—196° dec.). Three recrystallizations of this product from isopropanol-ethyl acetate (1:10 by volume) gave a screening sample of the desired product (m.p. 196—199° dec.).

The starting material used in this example was obtained as follows:

2-Chloro-5-trifluoromethylphenyl-thiourea

Anhydrous ammonia was bubbled with stirring through a solution of 2-chloro-5-trifluoromethylphenyl isothiocyanate (79.6 g) in ethyl acetate (800 ml) at ice-bath temperature for 4 hours; completion of the reaction was checked by lack of an isothiocyanate band in the I.R. spectrum on an aliquot. The resulting solution was filtered and evaporated to dryness under reduced pressure; the residue was recrystallized from benzene to give the desired product (39.9 g, m.p. 131—135°). Two recrystallizations of a sample from benzene gave purer product (m.p. 136—138°) which did not give satisfactory elementary analysis, but could be used satisfactorily for the next step.

2 - Chloro - 5 - trifluoromethylphenyl Cyanamide

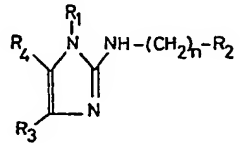
A boiling solution of 100 g of KOH (85%) in 240 ml water was added to a suspension of 2 - chloro - 5 - trifluoromethylphenyl - thiourea (0.152 mole, 39.9 g) in 240 ml of water. The resulting solution was immediately treated with a boiling saturated solution of lead acetate trihydrate (0.167 mole, 63.2 g) in water, adding it in a rapid stream with vigorous magnetic stirring. The mixture was boiled with vigorous stirring for 20 minutes, and cooled immediately to 0° with a salt-ice bath, the lead sulfide was filtered off with suction and washed with 100 ml of boiling 4% aqueous potassium hydroxide solution and boiling water. The filtrate was acidified with glacial acetic acid (100 ml) to pH 5 while maintaining the temperature at 0—5°. The resulting product (31.0 g, m.p. 116—120°) was filtered off. Recrystallization of a sample (1.0 g) from benzene (5 ml) gave an analytical sample of the desired product (m.p. 127—129°).

1 - (o - Chloro - m' - trifluoromethylphenyl)-3-(β,β-diethoxyethyl)guanidine

A solution of 2-chloro-5-trifluoromethylphenyl cyanamide (0.07 mole, 15.44 g) and aminoacetaldehyde diethylacetal (0.07 mole, 9.32 g) in anhydrous benzene (140 ml) was heated under reflux for 3 hours. The reaction mixture was cooled, filtered and the filtrate was evaporated to dryness to give the crude product (24.6 g, $n_D^{25} = 1.51$).

WHAT WE CLAIM IS:—

1. Process for the production of new imidazole derivatives of the general formula I

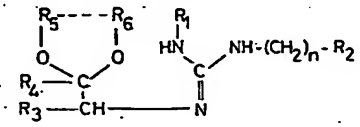


(I)

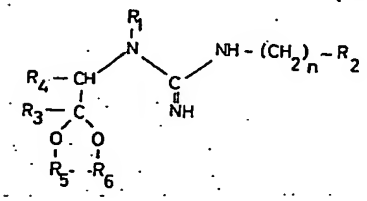
and tautomeric forms thereof,
wherein
n represents 0, 1 or 2, and of
R_1 and R_2 one represents hydrogen while the other represents phenyl, unsubstituted, or

mono- or disubstituted by, independently of each other, halogen, alkyl having at most 6 carbon atoms, alkoxy having at most 4 carbon atoms or trifluoromethyl

R_3 and R_4 each represent hydrogen or alkyl having at most 6 carbon atoms, and pharmaceutically acceptable acid addition salts thereof, and characterised by cyclisation of a compound of the general formula IIa or IIb



(IIa)

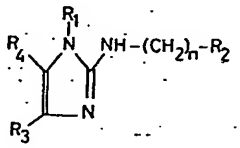


(IIb)

or a tautomeric form or acid addition salt thereof, wherein

R_1, R_2, R_3, R_4 and n have the meanings given above, and R_5 and R_6 each represents alkyl having at most 6 carbon atoms or together alkylene having at most 3 carbon atoms, by means of an acid, and isolation of the product in form of an acid addition salt or as the free base, and, if desired, converting the free base into a salt with an inorganic or organic acid.

2. Compounds of the general formula I



(I)

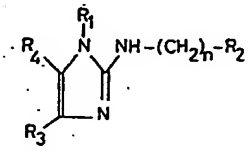
and its tautomeric forms, wherein

n represents 0, 1 or 2, and of

R_1 and R_2 one represents hydrogen while the other represents phenyl, unsubstituted, mono- or disubstituted by, independently of each other, halogen, alkyl having at most 6 carbon atoms, alkoxy having at most 4 carbon atoms or trifluoromethyl, and

R_3 and R_4 each represent hydrogen or alkyl having at most 6 carbon atoms, and pharmaceutically acceptable acid addition salts thereof.

3. Compounds of the general formula Ia



(Ia)

and its tautomeric forms, wherein

n represents 0,

R_1, R_3 and R_4 represent hydrogen, and

R_2 represents a phenyl group, mono- or disubstituted by, independently of each other, chlorine, bromine, alkyl, having at most 6 carbon atoms having at most 4 carbon atoms alkoxy or trifluoromethyl.

4. Process for the production of compounds of the general formula I, defined in claim 1, as herein described with reference to and as illustrated in any of the foregoing examples.

5. Compounds of the general formula I, defined in claim 2, as herein described with reference to and as illustrated in any of the foregoing examples.

6. Pharmaceutical compositions containing a compound of the general formula I or a pharmaceutically acceptable acid addition salt thereof together with at least one inert carrier.

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